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INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***759/Del/02*** *dated* ***19th July 2002.***

Witness my hand this 09th Day of September 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

23 AUG 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF SUMATRIPTAN TABLETS"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. RAJEEV SHANKAR MATHUR

b. T. VIJAYA KUMAR

c. SUNILENDU BHUSHAN ROY

d. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

DUPLICATE

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501 - 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, RAJEEV SHANKAR MATHUR, T. VIJAYA KUMAR, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(RAJEEV SHANKAR MATHUR)

b.

T. Vijaya Kumar.

(T. VIJAYA KUMAR)

c.

(SUNILENDU BHUSHAN ROY)

d.

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **683128** dated **09.07.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **19TH** day of **July, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

959/2002

FORM 2

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

A PROCESS FOR THE PREPARATION OF UNCOATED SUMATRIPTAN TABLETS

RANBAXY LABORATORIES LIMITED

19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of sumatriptan tablets for oral administration.

Sumatriptan and its physiologically acceptable salts have unpleasant taste. Sumatriptan and its salt when administered orally may intensify the nausea and vomiting associated with migraine. A successful masking of the unpleasant taste is a key element for acceptance and patient's compliance of an oral dosage form.

Prior art researchers have used different techniques to mask the unpleasant taste of sumatriptan.

The PCT application WO 01/37816 discloses a process for the coating of tablet cores comprising spraying a coating solution or suspension comprising a sugar, or a starch, or a mixture of a sugar and a starch, on to the tablet cores, with the proviso that film-forming agents in the suspension or solution is excluded, to obtain coated tablets.

United States patent No. 5,863,559 discloses a film coated solid dosage form of sumatriptan, such as a film coated tablet comprising a tablet core containing sumatriptan or a pharmaceutically acceptable salt or solvate thereof as active ingredient, substantially covered with a coating comprising film forming polymers, such as hydroxypropyl methylcellulose, hydroxypropyl cellulose or methylcellulose, and copolymers of methacrylic acid and methyl methacrylate polymers.

In the above approaches it is the coating over the core tablets, which is responsible for masking the bitter taste of drug.

Film coating should have good film properties and tensile strength, so that it withstands mechanical stress occurring during processing, packing, transport and storage. Moreover, the solution of the film-forming polymer must thoroughly wet the surface of the tablets core and therefore must be finely atomized to spread well. Hence, only low concentrations of viscous film formers such as hydroxypropyl methylcellulose (HPMC) can be employed which results in long processing times and high costs. HPMC has further disadvantages, in the wetting characteristics; adhesiveness to the tablet surface;

pigment binding capacity, mechanical properties of the film; hygroscopicity; permeability to water vapor and oxygen and difference in disintegration times between film coated tablets and core.

Similarly sugar coating is a tedious process, moreover it is hygroscopic and requires more weight build up to be effectively taste mask.

Moreover for conventional dosage forms, it is important that the disintegration of tablet and release of the active ingredient is not influenced by the coating.

We have now discovered a simple and economic process, which effectively mask the unpleasant taste of sumatriptan, without the need of any type of coating.

Therefore the present invention provides a process for the preparation of uncoated sumatriptan tablet for oral administration comprising the steps of:

a. preparing granules by granulating sumatriptan and/or its physiologically acceptable salt alone or in combination with diluent and/or binder with organic solvent or a solution/suspension of diluent and/or binder in oraganic solvent, such as herein described;
b. blending the granules with pharmaceutically acceptable excipient such as herein described;
c. compressing the blend to form a tablet; and
d. optionally polishing the tablet by
    i. sprinkling a fine powder grade of wax material, or
    ii. spraying a solution/suspension of wax material in organic solvent such as herein described.

For the purpose of the present invention granulation may be carried out by dry mixing the diluent and/ or binder with sumatriptan, and granulating with aqueous and/or non-aqueous solvent. Alternatively sumatriptan may be granulated with an aqueous and/or non-aqueous solution / suspension of diluent and / or binder. Aqueous solvent may be water where as non-aqueous solvent may be alcohol and isopropyl alcohol.

These sumatriptan granules may be mixed with other pharmaceutically acceptable excipients and filled into a capsule or compressed to form a tablet. The tablets may be further wax polished by spraying a solution /suspension of wax on to the tablets.

The process of present invention avoids the coating step and thereby reduce the processing time and cost. Granulation with the diluent and/ or binder provides a uniform coat on to the individual sumatriptan particles and thereby masks the unpleasant taste. Wax polishing provides further taste masking, less tablet to tablet picking, good stability in storage and aesthetic appeal to the tablet. It also reduces dust formation, which occurs during packaging of the tablets.

For the purpose of the present invention the term "Sumatriptan" includes sumatriptan and its physiologically acceptable salts. Such salts include salts of inorganic or organic acids such as hydrochloride, hydrobromide, sulphate, nitrate, phosphate, formate, mesylate, citrate, benzoate, fumarate, maleate, tartrate and succinate salts.Sumatriptan succinate salt (1:1) is preferred.

Diluent(s) of the present invention may be selected from calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and mixtures thereof.

Binders of the present invention may be selected from methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, alginate and the like.

Other pharmaceutically acceptable excipients of the present invention may include disintegrant, lubricant, coloring agent and flavoring agents.

Disintegrant of the present invention may be selected from low substituted hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose,

sodium carboxymethyl cellulose, croscarmellose sodium A-type (Ac-di-sol), starch, crystalline cellulose, hydroxypropyl starch, partly pregelatinized starch and the like.

Lubricant of the present invention may be selected from stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax and the like.

Coloring agents and flavoring agents may be selected from any approved FDA colors and flavors.

Wax polish of the present invention comprises a waxy material. Suitable waxy material may be selected from shellac, modified shellac (opaglos), Opaglos II, carnuba wax, bees wax, paraffin wax, polyethylene glycol, and the like. One application is usually sufficient to obtain the desired effect. Preferred total weight build up of wax polishing solid is up to 10% w/w, based on the weight of the tablet.

Wax polishing is carried out by either sprinkling the fine powder grade of wax or spraying the solution / suspension of wax materials using any suitable spray equipment. Wax solution or suspension is prepared using organic solvents such as ethanol, acetone, carbon tetrachloride, isopropyl alcohol, naphtha, dichloromethane and the like. The quantity of the solvent may vary according to the wax material, equipment and the conditions used.

The process of present invention may be carried out by blending sumatriptan or its physiologically acceptable salt with half quantity of diluent and or binder, granulating the blend with the solvent. Drying the granules and sifting to get the desired size. Mixing the dried granules with rest of the diluent, binder, disintegrant and lubricant. Compressing the blend to make tablets.

Alternatively sumatriptan may be granulated with a diluent and/ or binder dissolved or suspended in an appropriate solvent.

These uncoated tablets may be wax polished by spraying the wax solution / suspension using airless spray equipment. Wax polished tablets are either air dried or tray dried.

The present invention is further illustrated by the following examples but they should not be construed as limiting the scope of the invention anyway.

EXAMPLE-1

INGREDIENTS	QUANTITY(mg/tablet)
INTRAGRANULAR	
Sumatriptan Succinate eq. to 100 mg Sumatriptan	140.0
Lactose Monohydrate	133.0
Purified Water	q.s.
EXTRAGRANULAR	
Microcrystalline cellulose	15.0
Croscarmellose sodium.	3.0
Magnesium Stearate	3.0
Talc	6.0
TOTAL WEIGHT	**300.0**

Process:

1. Sumatriptan Succinate is sifted through a suitable mesh along with half quantity of Lactose and blended for 30 minutes.
2. The blend was granulated using Purified water.
3. Granules were dried at 60°C.
4. Dried granules were passed through suitable mesh.
5. Granules were mixed with sifted Lactose (rest of the quantity), Microcrystalline cellulose and Croscarmellose sodium for 20 minutes.

6. Granules of step 5 mixed with Magnesium stearate and talc for 5 minutes.
7. The bend of step 6 was compressed using suitable tooling.

EXAMPLE-2

INGREDIENTS	QUANTITY (mg/tablet)
INTRAGRANULAR	
Sumatriptan Succinate eq. to 100 mg Sumatriptan	140.0
Lactose Monohydrate	128.0
Purified Water	q.s.
EXTRAGRANULAR	
Microcrystalline cellulose	32.5
Croscarmellose sodium	6.0
Magnesium Stearate	4.5
Talc	3.0
Colloidal Anhydrous Silica	3.0
TOTAL WEIGHT	**300.0**

Process:

1. Lactose was dispersed in purified water.
2. Sumatriptan succinate was charged in a fluid bed processor and sprayed with the lactose dispersion by top / bottom / tangential spray to obtain granules.
3. Granules mixed with remaining tablet excipients and compressed.

EXAMPLE- 3

INGREDIENTS	QUANTITY (mg/tablet)
INTRAGRANULAR	
Sumatriptan Succinate eq. to 100 mg Sumatriptan	140.0
Hydroxyproplyl methylcellulose	20.0

Purified Water	q.s.
EXTRAGRANULAR	
Lactose Monohydrate	108.0
Microcrystalline cellulose	32.5
Croscarmellose sodium	6.0
Magnesium Stearate	4.5
Talc	3.0
Colloidal Anhydrous Silica	3.0
TOTAL WEIGHT	**300.0**

Process:

1. Hydroxypropyl methylcellulose was dispersed in purified water.
2. Sumatriptan succinate was charged in a fluid bed processor and sprayed with the hydroxypropyl methylcellulose dispersion by top / bottom / tangential spray to obtain granules.
3. Granules were mixed with remaining tablet excipients and compressed.

EXAMPLE 4

INGREDIENTS	**QUANTITY (mg/tablet)**
INTRAGRANULAR	
Nonpareils seeds	100.0
Sumatriptan Succinate eq. to 100 mg Sumatriptan	140.0
Lactose	100.0
Hydroxyproplyl methylcellulose	20.0
Purified Water	q.s.
EXTRAGRANULAR	
Microcrystalline cellulose	17.5
Croscarmellose sodium	12.0
Magnesium Stearate	4.5
Talc	3.0
Colloidal Anhydrous Silica	3.0
TOTAL WEIGHT	**400.0**

Process:

1. Sumatriptan and lactose were dispersed in purified water.
2. Nonpareils seeds were charged in a fluid bed processor and sprayed with the sumatriptan and lactose dispersion by top / bottom / tangential spray.
3. Hydroxypropyl methylcellulose was dispersed in purified water.
4. Hydroxypropyl methylcellulose dispersion was sprayed by top / bottom / tangential spray on nonpareils coated with sumatriptan and lactose.
5. Coated nonpareils were mixed with remaining tablet excipients and compressed.

Tablets prepared by Examples 1-4 were wax polished using any of the following techniques.

1. Carnuba Wax – 0.5 – 2.0 mg / tablet
   Sumatriptan tablets were charged in a polishing pan, warmed to 40 - 45° C and sprinkled with fine powder grade of Carnuba wax under rolling. Rolling is continued till uniform polishing is achieved.

2. Carnuba Wax – 0.5 – 2.0 mg/ tablet
   Carbon tetrachloride - qs
   Carnuba wax was dissolved in sufficient quantity of Carbon tetrachloride and applied on Sumatriptan tablets in a polishing pan under a hot stream of air (40 – 45°C).

3. Polyethylene glycol – 0.5 – 2.0 mg / tablet
   Isopropyl alcohol – qs
   Methylene chloride – qs
   Polyethylene glycol was dissolved in a solution containing equal amounts of Isopropyl alcohol and methylene chloride and applied on Sumatriptan tablets in a polishing pan under a hot stream of air (40 – 45°C).

4. Carnuba Wax – 0.5 – 2.0 mg
   White wax - 0.25 – 1.0 mg
   Carbon tetrachloride – qs

Carnuba wax and [redacted]hite wax (2:1 preferred ratio) were [redacted]ssolved in sufficient quantity of Carbon tetrachloride and applied on Sumatriptan tablets in a polishing pan under a hot stream of air (40 – 45°C).

5. Opaglos

Sumatriptan tablets were charged in a polishing pan and polished using opaglos.

WE CLAIM:

1. A process for the preparation of uncoated sumatriptan tablet for oral administration comprising the steps of:
    a. preparing granules by granulating sumatriptan and/or its physiologically acceptable salt alone or in combination with diluent and/or binder with organic solvent or a solution/suspension of diluent and/or binder in oraganic solvent, such as herein described;
    b. blending the granules with pharmaceutically acceptable excipient such as herein described;
    c. compressing the blend to form a tablet; and
    d. optionally polishing the tablet by
    i. sprinkling a fine powder grade of wax material, or
    ii. spraying a solution/suspension of wax material in organic solvent such as herein described.

2. The process of claim 1 wherein physiologically acceptable salt of sumatriptan may be selected from the group consisting of hydrochloride, hydrobromide, sulphate, nitrate, phosphate, formate, mesylate, citrate, benzoate, fumarate, maleate, tartarate and succinate salts.

3. The process of claim 2 wherein physiologically acceptable salt is sumatriptan succinate (1:1).

4. The process of claim 1 wherein diluent is selected from the group consisting of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners.

5. The process of claim 4 wherein diluent is lactose.

6. The process of claim 1 wherein binder is selected from the group consisting of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose,

polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, alginate.

7. The process of claim 6 wherein binder is hydroxypropyl methylcellulose.

8. The process of claim 1 wherein pharmaceutically acceptable excipients may be selected from diluent, binder, disintegrant, lubricant, coloring agent and flavoring agent.

9. The process of claim 8 wherein disintegrant is selcted from the group consisting of low substituted hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium, starch, crystalline cellulose, hydroxypropyl starch, partly pregelatinized starch.

10. The process of claim 9 wherein disintegrant is crosscarmellose sodium.

11. The process of claim 8 wherein lubricant is selected from the group consisting of stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax.

12. The process of claim 11 wherein lubricant is a mixture of talc and magnesium stearate.

13. The process of claim 1 wherein aqueous solvent is water.

14. The process of claim 1 wherein non-aqueous solvent is alcohol or isopropyl alcohol.

15. The process of claim 1 wherein wax material is selected from the group consisting of shellac, modified shellac (opaglos), opaglos II, carnuba wax, bees wax, paraffin wax, polyethylene glycol.

16. The process of claim 15 wherein wax material is modified shellac.

17. The process of claim 15 wherein wax material is polyethylene glycol.

18. The process of claim 1 wherein the total weight buildup of wax material is up to 10% w/w, based on the weight of tablet.

19. The process of claim 1 wherein organic solvent is selected from the group consisting of ethanol, acetone, carbon tetrachloride, isopropyl alcohol, naphtha, dichloromethane.

20. A process for the preparation of uncoated sumatriptan tablet for oral administration, comprising the steps of preparing granules of sumatriptan with diluent and/or binder, mixing with pharmaceutically acceptable excipient, and compressing into tablet substantially as described and illustrated by the examples herein.

Dated this 19TH day of July, 2002.

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

A process for the preparation of uncoated sumatriptan tablet for oral administration comprising the steps of preparing granules of sumatriptan, diluent and/or binder; and compressing into tablet. The tablet may optionally be polished with a waxy material.